tion of the procedure was used to synthesize **α-bromophenylacetaldehyde dibenzylacetal**. An equimolar mixture of α-bromophenylacetaldehyde dimethylacetal and benzyl alcohol containing a few drops of concentrated sulfuric acid was placed in a flask equipped with a short-path distillation apparatus. The mixture was heated at 60–70° at 35 mm for 2.25 hr. During this time an 80% yield of methanol collected in the cold receiving flask. The contents of the reaction flask solidified on cooling. The solid was taken up in a large volume of carbon tetrachloride and washed with dilute potassium carbonate solution, dried over potassium carbonate, filtered, and concentrated under vacuum to yield an off-white solid. One recrystallization from absolute ethanol afforded a crystalline solid, mp 84–85°, in 69% yield.

D. **From α-Bromo-β-alkoxystyrenes.**—Some of the α-bromophenylacetaldehyde acetals obtained contained varying amounts of the corresponding α-bromo-β-alkoxystyrenes. Such an impure product was dissolved in the appropriate alcohol and treated with a few drops of concentrated sulfuric acid. The resulting mixture was allowed to stand for 2 to 7 days followed by the usual work-up. The product thus obtained was free of the styryl impurity.

E. **From Mixtures of Various Compounds.**—A bottle containing 100 ml of an alcohol and a few drops of concentrated sulfuric acid was maintained into which forerun fractions from distillations of various α-bromophenylacetaldehyde acetals and fractions of the mixed acetals containing the α-bromo-β-alkoxystyrenes were placed. After a period of 1 to 12 weeks, the alcoholic solution was heated under a 15-cm Vigreux column until about 70% of the alcohol had distilled. A fresh quantity of the alcohol was added and the mixture was allowed to stand at room temperature for 1 to 2 weeks. After this time the normal work-up was employed to yield the product. This method was used for preparing the di-*n*-propyl-, diisopropyl-, and di-*sec*-butylacetals.

Synthesis of Phenylketene Acetals.—The general procedure employed for synthesizing the diprimary, primary–secondary, and cyclic acetals was essentially that used by McElvain and Curry[12] for preparation of some of these phenylketene acetals. A solution of potassium *t*-butoxide was prepared by dissolving 1.7 g (0.044 mole) of potassium in 36 ml of *t*-butyl alcohol. The appropriate α-bromophenylacetaldehyde acetal (0.04 mole) was added and the mixture was heated under a Vigreux column equipped with a short-path distillation apparatus at such a rate that most of the *t*-butyl alcohol distilled over a 2- to 4-hr period. The last of the *t*-butyl alcohol was removed at reduced pressure and the product was distilled rapidly at 0.1 to 1.0 mm using only the short-path distillation apparatus. Slow redistilllation from calcium hydride gave the pure product. The purity of most of the phenylketene acetals was estimated by vpc analyses on a 1.5-m Apiezon L column at 180–190°.

For disecondary or primary–tertiary acetals, a 4–15-hr reflux period was employed. The crude products obtained were contaminated with varying amounts of the normal and ortho esters, starting material, and α-bromo-β-alkoxystyrenes. Further distillation yielded 70–80% pure material.

3-Ethoxy-1H-benzopyran was prepared as were the diprimary and primary–secondary acetals except that a shorter heating time (0.5 to 1 hr) was employed.

Excess potassium *t*-butoxide (3.1 equiv) and a 16–23-hr-reflux period were used for the preparation of **phenylketene divinyl acetal**. The crude product (49%) obtained contained significant amounts of various partially dehydrobrominated products. The divinyl acetal was easily separated in pure conditions by distillation (15% yield).

Two attempts were made to prepare phenylketene diallyl acetal. The normal procedure gave some product lacking the characteristic strong ultraviolet absorption appropriate to a phenylketene acetal. In the second attempt, the bromo compound was stirred with a potassium *t*-butoxide solution at room temperature. No increase in absorption at 265 mμ was observed.

No phenylketene dibenzyl acetal was obtained when the appropriate α-bromo acetal was treated with a potassium *t*-butoxide solution both at 25 and 60° as determined by ultraviolet monitoring.

Catalytic Hydrogenation. II. A New, Convenient Technique for Laboratory Hydrogenations. A Simple, Automatic Device for Atmospheric Pressure Hydrogenations

CHARLES A. BROWN AND HERBERT C. BROWN

R. B. Wetherill Laboratory, Purdue University, Lafayette, Indiana

Received June 10, 1966

The rapid, *in situ* preparation of highly active hydrogenation catalysts by the reduction of platinum metal salts with sodium borohydride has been combined with a convenient automatic hydrogen generator based on sodium borohydride to provide a new highly convenient procedure for laboratory-scale hydrogenations. The utility of the new platinum-on-carbon catalyst and the applicability of the new hydrogenation technique have been explored over a wide range of representative hydrogenation problems. It is concluded that the new technique possesses a number of significant advantages for laboratory-scale hydrogenations.

For nearly one-half century the low-pressure hydrogenator has been a valuable tool to the synthetic organic chemist. For all its virtues, however, the low-pressure hydrogenator in its usual form—hydrogen reservoir, control valves, heavy-walled glass reaction bottle and shaker—possesses a number of disadvantages. (1) It requires a reasonably permanent set-up with a consequent loss of laboratory space for other purposes. (2) The apparatus requires a hydrogen cylinder and often a purification train for the gas. (3) The apparatus operates with pressure in a glass bottle and with a consequent danger from fast internal pressure build-ups during exothermic reactions. (4) It is not well suited for following quantitatively the hydrogen uptake, and, since the pressure changes during the reaction, really meaningful rate data cannot be obtained. (5) It is relatively inconvenient to cool the shaking reaction vessel, making difficult hydrogenations at reduced temperatures. (6) Finally, in its usual form, the apparatus possesses a quite limited capacity.

In the course of a study of the new hydrogenation catalysts, readily produced by the reaction of sodium borohydride with platinum salts,[1] we developed a new, convenient technique for low-pressure hydrogenations.[2,3] This technique utilized the acidic hydrolysis of sodium borohydride solutions to produce hydrogen as required to maintain the pressure at the desired level. This allowed the entire quantity of hydrogen for 1 mole of olefin to be stored in as little as 100 ml of solution. To utilize fully this new, convenient method of hydrogen supply, a simple glass apparatus assembled

(1) H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **84**, 1494 (1962).
(2) C. A. Brown and H. C. Brown, *ibid.*, **84**, 1495 (1962).
(3) H. C. Brown and C. A. Brown, *Tetrahedron*, in press.

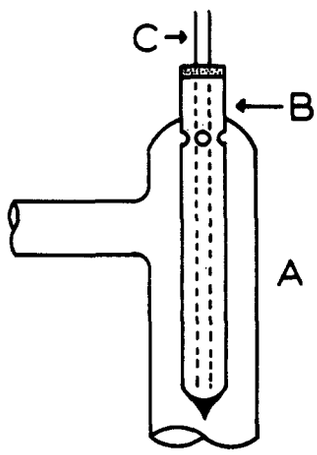


Figure 1.—Automatic hydrogenator valve: A, outer tube; B, mercury well; C, delivery tube.

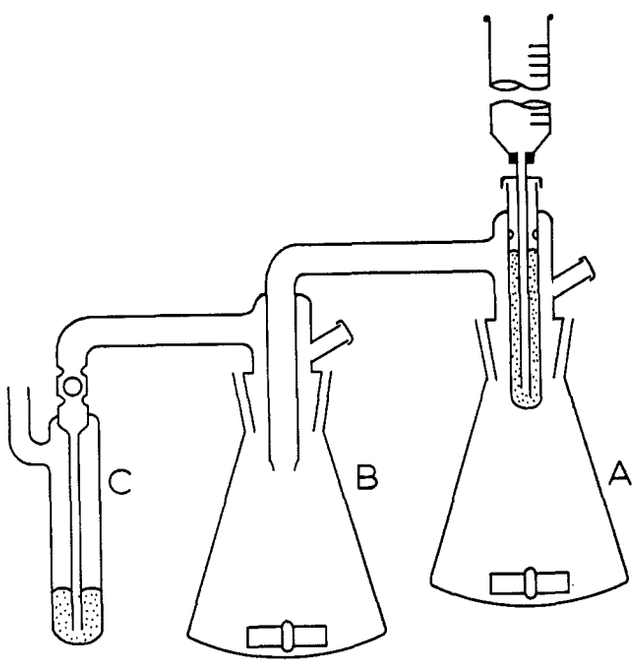


Figure 2.—Hydrogenator assembled for external hydrogen generation: A, generator; B, reactor; C, bubbler with back-up prevention valve.

with gas-tight joints was developed. This device, with the hydrogen source, overcame the objections to previous hydrogenators. (1) It could be assembled in a matter of minutes on any desk. (2) Sodium borohydride, a compact, stable chemical, is used as the hydrogen source. The hydrogen produced from this material is very pure. (3) The new apparatus operates at atmospheric pressure, sealed only with a mercury bubbler. Excess pressure from a runaway reaction is vented before explosive pressure build-ups can occur. (4) Since sodium borohydride solutions may be readily standardized, hydrogen uptake may be measured to 1% accuracy. This is very useful in the partial hydrogenation of polyunsaturates. Furthermore, the constant-pressure operation allows for more meaningful rate data. (5) Hydrogenations of labile materials at low temperatures are readily performed. (6) The apparatus does not appear to have any serious limitations in capacity. As much as 2000 g of material has been hydrogenated in the apparatus without special difficulty. Accordingly, we undertook to explore the range of applicability of this new hydrogenation procedure.

Results

Originally the addition of the sodium borohydride solution to the generator was manually controlled. However, this proved rather tedious and we undertook to find an automatic regulator. Eventually, a simple mercury valve was developed (Figure 1). The valve consists of an outer tube (A), a mercury well (B), and a delivery tube (C), connected to the mercury well B by a gas-tight seal. Outer tube A is fastened to the gas generator of the hydrogenator. The mercury well is filled with mercury to just below the vent holes at the top. Delivery tube C is sealed to the top of B and passes well below the mercury level. A 4-in. 17- or 19-gauge hypodermic needle is used for the delivery tube, and a rubber stopple seals the top of the mercury well. A syringe barrel or a buret containing sodium borohydride solution is attached to the needle. The amount of mercury in the well is adequate to support the column of sodium borohydride solution. When the pressure of the system drops several millimeters due to the absorption of hydrogen by the substrate, borohydride solution is drawn from the syringe or buret into the generator flask where it reacts with the acidic solution liberating hydrogen. The increased hydrogen pressure causes the flow of borohydride to cease. Thus borohydride solution is added automatically at a rate adequate to maintain the system at essentially atmospheric pressure.[4]

The assembled apparatus is shown in Figure 2. The hydrogen is generated in the flask at the right (A) with borohydride supplied from the buret. Hydrogen gas is passed into the reactor flask in the center (B) where it is absorbed by the magnetically stirred substrate. The bubbler at the left (C) allows gas to escape during flushing. It has a ball valve at the top to prevent mercury from being sucked back into the reactor if the valve should become clogged.[5]

In an alternative procedure, hydrogen may be generated directly in the reactor flask. Figure 3 shows the apparatus thus assembled.[6]

The use of a buret in place of a syringe allows the reaction to be followed readily with an accuracy of 1%. Smooth, vibrationless stirring is facilitated by the rounded bottoms of the flasks and the large spin-rings on the stirring bars. These rings allow the bar to spin smoothly with little tendency to wander from the center.

Briefly, the external hydrogenation procedure is as follows. Chloroplatinic acid solution, activated carbon, and a magnetic stirring bar are placed in ethanol solvent in the reactor. The flask is attached to the system which is then purged with nitrogen. With stirring, sodium borohydride solution is injected into the reactor through the injection port, followed by hydrochloric acid, or, if circumstances make it prefer-

(4) C. A. Brown and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 2829 (1962).

(5) Commercial models of these automatic hydrogenators, both preparative and analytical, are currently available from the Delmar Scientific Laboratories, Maywood, Ill.

(6) Separate generation and hydrogenation is known as "external hydrogenation," combined hydrogenation and generation is known as "internal hydrogenation."

able, a weak acid, acetic acid.[3,7] Borohydride solution injected into the generator purges the system with hydrogen, and then the substrate is injected into the reactor. This *in situ* generation of the catalyst and its utilization without isolation avoids possible poisoning by exposure to contaminated atmospheres.

To test the utility of the procedure and apparatus, a series of hydrogenations was carried out on 40.0 mequiv of various unsaturated hydrocarbons.

First, the unsaturated hydrocarbons were reduced over 0.20 mmole of platinum on 1.0 g of carbon support by the internal hydrogenation procedure. All of the compounds examined were readily reduced. The results are summarized in Table I.

TABLE I

INTERNAL HYDROGENATION OF VARIOUS OLEFINS[a]

Compound	$T_{100\%}$,[b] min
1-Octene	4
2-Octene	4.5
2,4,4-Trimethyl-1-pentene	4.5
2,4,4-Trimethyl-2-pentene	6
Cyclohexene	5.5
Cyclooctene	14
Styrene	10
3-Hexyne	6.5
4-Vinylcyclohexene	6
Benzene	32% in 1 hr

[a] Internal hydrogenation of 40.0 mequiv of substrate over 0.20 mmole of platinum on 1.0 g of carbon at 25°, 1-atm pressure. [b] Time for complete absorption of hydrogen. Total hydrogen absorbed is 896 cc at STP.

External hydrogenations also proceed readily, although somewhat more slowly than the corresponding internal hydrogenations. These results are summarized in Table II.

TABLE II

EXTERNAL HYDROGENATION OF OLEFINS[a]

Compound	$T_{50\%}$,[b] min	$T_{100\%}$,[b] min
1-Octene	4.5	9
2,4,4-Trimethyl-2-pentene	5	10.5
Cyclohexene	5.5	11
Limonene[c]	6	17
1,3-Cyclooctadiene[c]	6	15.5
1,5,9-Cyclododecatriene	9	18

[a] Hydrogenation of 40.0 mequiv of substrate over 0.20 mmole of platinum on 1.0 g of carbon at 25°, 1-atm pressure. [b] Time for half and complete uptake of hydrogen. Total uptake at STP is 896 cc. [c] These reductions showed a slowing in rate at approximately 50% reduction. Before and after this point, the reactions were nearly linear.

It was of interest to determine if the catalyst would be affected by the presence of various functional groups in the molecule. All of the unsaturated compounds examined hydrogenated readily except for cyclohexene-4-carboxaldehyde, which poisoned the catalyst. These results are summarized in Table III.

Finally we determined the effect of having various functional groups conjugated with the double bond. The results, summarized in Table IV, revealed that the large majority of such compounds can be hydrogenated without difficulty. Cinnamaldehyde and crotonitrile caused catalyst poisoning. The 1-penten-3-ol absorbed about 10% over the theoretical amount of hydrogen necessary for the double bond, indicating some hydrogenolysis. Usually hydrochloric acid was present in all of the hydrogenations. However, the hydrogenation of benzalacetone required acetic acid; otherwise, about 30–40% of the substrate was hydrogenolyzed to the alcohol and the hydrocarbon.

(7) H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **84**, 2827 (1962).

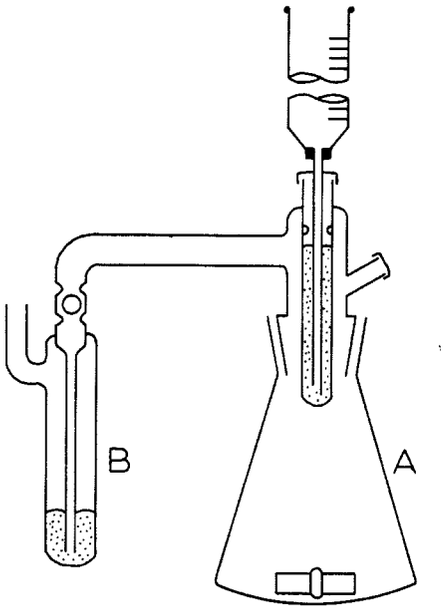


Figure 3.—Hydrogenator assembled for internal hydrogen generation: A, generator and reactor; B, bubbler with back-up prevention valve.

TABLE III

HYDROGENATION OF UNSATURATED COMPOUNDS (NONCONJUGATED)[a]

Substituent	Compound[b]	$T_{100\%}$,[c] min
Acid	Allylacetic acid	14.5
Ester	Ethyl oleate	11.5
Aldehyde	Cyclohexen-4-carboxaldehyde	Poisoned
Ketone	2-Methyl-2-hepten-6-one	18
Nitrile	Allyl cyanide	22
Phenyl	Allylbenzene	12
Alcohol	Ethyl ricinolate	16

[a] See Table II. [b] Reduction of olefinic double bonds only. [c] Time for complete reduction.

TABLE IV

HYDROGENATION OF UNSATURATED COMPOUNDS (CONJUGATED)[a]

Substituent	Compound[b]	$T_{100\%}$,[c] min
Acid	Crotonic acid	13
Ester	Ethyl crotonate	11
	Diethyl maleate	14.5
Aldehyde	Cinnamaldehyde	Poisoned
Ketone	Mesityl oxide	13
	Benzalacetone[d]	32
Nitrile	Crotonitrile	Poisoned
Phenyl	Styrene	15.5
Alcohol	1-Penten-3-ol	12

[a] See Table II. [b] Hydrogenation of olefinic double bond only. [c] Time for complete absorption of hydrogen. [d] Acetic acid was used in the reactor since the standard HCl causes excessive hydrogenolysis of the ketone function.

In all cases where the catalyst was not poisoned, the hydrogenations proceeded nearly linearly, the rate

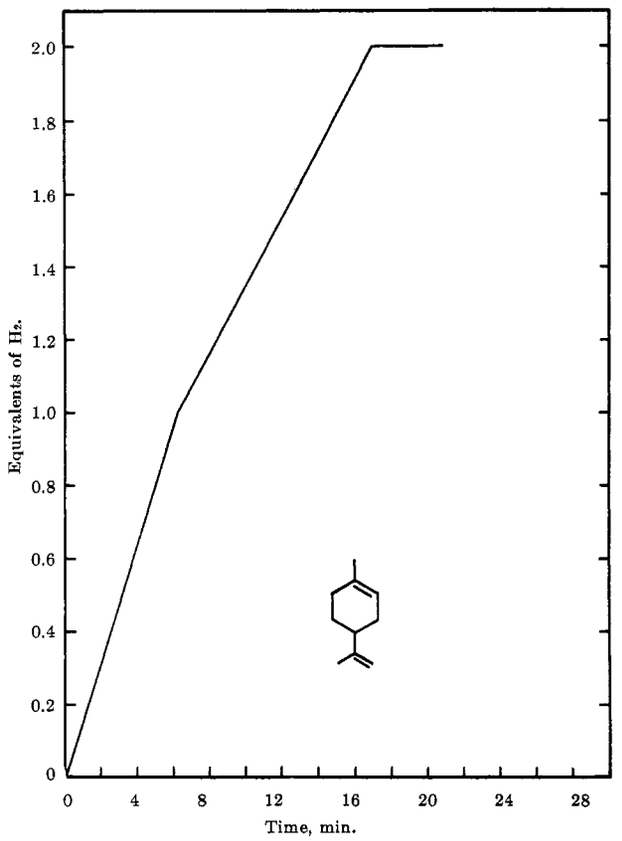


Figure 4.—Hydrogenation of *d*-limonene over carbon-supported platinum.

toward the end rarely being 25% less than at the beginning.

So far we had used ethanol exclusively as the hydrogenation solvent; it was the solvent for the preparation of the catalyst. However, in some cases other solvents would be desirable, especially if the substrates were sensitive to protonic media or were sparingly soluble in ethanol. Consequently, the hydrogenation of 1-octene was carried out in various solvents. The catalyst was prepared as usual in ethanol, but was washed free of ethanol with the desired solvent on a Büchner funnel and then washed into a hydrogenation flask (at no time was the catalyst allowed to go dry). As a blank, this procedure was carried through with ethanol as the wash solvent to provide a true basis for comparison of rates. The results (see Table V) revealed that methanol, ethanol, isopropyl alcohol, acetic acid, ethyl acetate, tetrahydrofuran and diglyme were suitable solvents for such hydrogenations.

TABLE V

EFFECT OF SOLVENT UPON THE HYDROGENATION OF 1-OCTENE OVER PLATINUM[a]

Solvent	$T_{50\%}$,[b] min	$T_{100\%}$,[b] min
Methanol	5.5	11
Ethanol	5.5	10.5
Isopropyl alcohol	6	12
Acetic acid	4.5	9
Tetrahydrofuran (THF)	5	10
Ethyl acetate	4	8
Diglyme	7.5	15
Dimethylformamide	Poisoned	
Acetonitrile	Poisoned	

[a,b] See Table II.

Dimethylformamide and acetonitrile poisoned the catalyst. Diglyme caused an appreciable uniform slowing (as opposed to poisoning) of the reaction. Acetic acid and ethyl acetate proved to be very useful hydrogenation solvents, the reduction of 1-octene being appreciably faster in these solvents than in ethanol. These results indicate the feasibility of using solvents other than ethanol, permitting the reduction of anhydrides, acid halides, and other proton-sensitive compounds. Again the rates of hydrogenation were linear.

The convenient control of temperature in this procedure encouraged us to examine the effect of low temperatures, 0 and −25°, on a number of hydrogenations. First, it is of interest that the observed times required for hydrogenation are not greatly increased at the lower temperatures. Thus, under the conditions described in Table II, 1-octene, which required 9.0 min at 25°, was hydrogenated in 13.0 min at 0° and in 24 min at −25°. Isomerization of residual olefin over platinum[3] was treatly reduced at low temperature. Thus, at 50% hydrogenation, the residual 1-pentene at 25° is 10% isomerized to 2-pentene, whereas at −25° there is only 1% of the isomerized material. We are currently exploring the utility of low temperatures for selective hydrogenations.

We next explored a number of representative hydrogenations on a relatively large scale.

First, the internal hydrogenation procedure was tested with 1-octene and diethyl maleate. The following results were obtained (compound, amount, time for reduction, isolated yield): 1-octene, 500 mmoles, 60 min, 77%; diethyl maleate, 500 mmoles, 70 min, 90%. These hydrogenations were carried out in the presence of hydrochloric acid. In fact, diethyl maleate hydrogenates sluggishly in the absence of strong acid. However, in some cases, strong acid causes undesirable isomerizations and rearrangements. Therefore, acetic acid was used during the hydrogenation of β-pinene. Five hundred millimoles was reduced in 2 hr, the last 10% reducing much more slowly than the first 90% (due to isomerization to α-pinene which is more difficult to hydrogenate). A yield of 87% was obtained, consisting of about 80% *cis*-pinane. In all of the above reactions 0.20 mmole of platinum catalyst on carbon was used for each 100 mmoles.

Next a series of external hydrogenations was carried out. Five hundred millimoles of ethyl oleate was hydrogenated in about 2 hr. Five hundred grams of this ester was reduced in 3.5 hr. Owing to poisoning, additional catalyst had to be added during the reaction. This was prepared as usual and injected as a slurry without opening the system, a convenient feature of this procedure. In both cases a yield of 90% of ethyl stearate was isolated.

The hydrogenation of 1,5,9-cyclododecatriene (150 mmoles) was carried out at 55–60° to keep the cyclododecane in solution. The reaction required about 1 hr and gave an 87% yield of cyclododecane. Since the reactor is stationary (being stirred magnetically instead of shaken) the temperature is easily controlled with a water or oil bath, or heating mantle.

To test the use of aprotic solvents, 500 mmoles of norbornen-5,6-dicarboxylic acid anhydride was hydrogenated in tetrahydrofuran solvent. An 89% yield of saturated anhydride was obtained in 1 hr.

Strong acid greatly promotes hydrogenolysis of benzalacetone during hydrogenation. Therefore, 500 mmoles of the compound was hydrogenated[8] in the absence of strong acid, yielding 460 mmoles (92%) of 93% pure benzylacetone, the impurities being mostly 1-phenyl-3-butanol with some *n*-butylbenzene. One hour was required for the reaction.

Literature procedures for low-pressure hydrogenations may also be carried out readily in the new apparatus. Following the procedure of Hershberg, *et al.*,[9] we hydrogenated 21.5 mmoles of cholesterol over 0.33 g of Adams catalyst in ethyl acetate containing a trace of perchloric acid. The reaction tailed off badly toward the end, 50% reduction occurring in 3 min, 100% in 20 min. (With 0.16 g of Adams catalyst the reaction requires about 1 hr for complete reduction.) An 81% yield of cholestanol was obtained.

One of the advantages of this apparatus is that the reaction can be followed quantitatively. This allows the operator to determine whether or not the reaction has reached the theoretical completion and, in the case of polyunsaturates, exactly when the desired equivalent amount of hydrogen has been absorbed. This is shown in the selective reductions of 1,3-cyclooctadiene and limonene. The hydrogenation of 40.0 mmoles of 1,3-cyclooctadiene yielded, by gas chromatography, 84% cyclooctene and 8% each of starting material and cyclooctane. The reduction of limonene was more selective, the products at 50% hydrogenation being 98% 1-methyl-4-isopropylcyclohexene, 1% limonene, and 1% saturated material (gas chromatographic analysis). The accuracy with which the reaction may be stopped can be seen from the analyses. The hydrogenation of limonene showed a distinct slowing in rate at 50% hydrogenation. With 1,3-cyclooctadiene the rate change was less distinct and appeared somewhat later in the reaction (see Figures 4 and 5). The results of the preparative hydrogenations are summarized in Table VI.

TABLE VI
PREPARATIVE HYDROGENATIONS

Compound	Procedure[a,b]	Solvent	Compd, mmoles	Time, min	Yield,[c] %
1-Octene	I	EtOH[d]	500	60	77
β-Pinene	I	EtOH[e]	500	120	87[f]
Diethylmaleate	I	EtOH[d]	500	70	90
Ethyl oleate	E	EtOH[d]	500	120	92
Ethyl oleate	E	EtOH[d]	1600	220	95
1,5,9-Cyclododecatriene[g]	E	EtOH[d]	150	60	87
Norbornene-5,6-dicarboxylic acid anhydride	E	THF[h]	500	60	90
Benzalacetone	E	EtOH[e]	500	60	92[i]
1,3-Cyclooctadiene	E	EtOH[d]	20	6	*j*
Limonene	E	EtOH[d]	20	6	*k*

[a] Internal (I) or external (E). [b] Hydrogenation at 25° except where otherwise indicated. [c] Isolated. [d] Hydrochloric acid present. [e] Acetic acid present. [f] Ratio of *cis*- to *trans*-pinane, 4:1. [g] 55°. [h] No acid present. [i] Gas chromatographic examination revealed 93% 1-phenyl-3-butanone. [j] Cyclooctane, 8%; cyclooctene, 84%; 1,3-cyclooctadiene, 8%. [k] 8,9-Dihydrolimonene, 98%; tetrahydrolimonene, 1%; 1,2-dihydrolimonene, 0%; limonene, 1%.

(8) A. H. Blatt, Ed., "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc.," New York, N. Y., 1941, p 101.

(9) E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle, and L. Kuhlen, *J. Am. Chem. Soc.*, **73**, 1144 (1951).

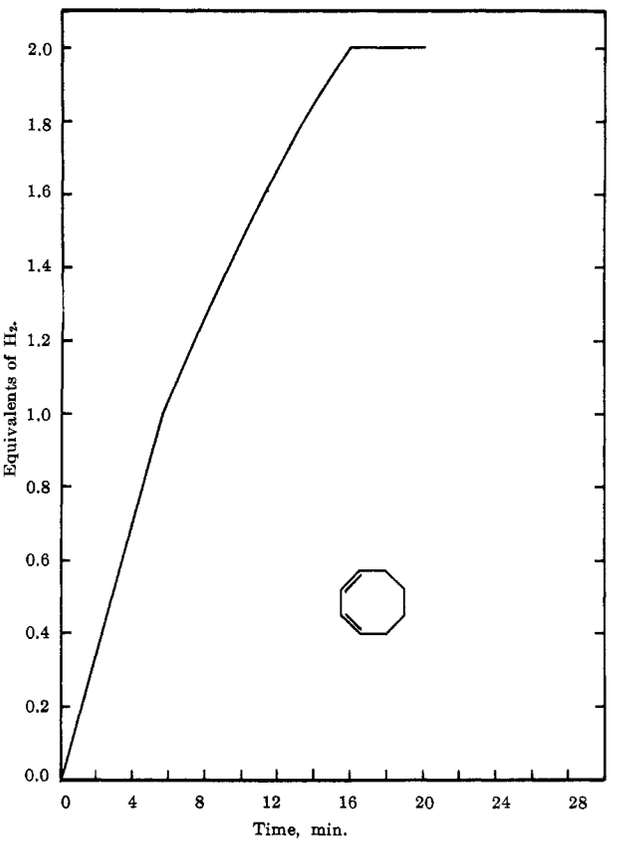


Figure 5.—Hydrogenation of 1,3-cyclooctadiene over carbon-supported platinum.

Discussion

The new hydrogenation technique provides a highly convenient method for performing laboratory hydrogenations. It permits many olefinic compounds to be readily reduced, and the rates of reduction followed simply and conveniently. Rates may be followed and partial hydrogenations may be stopped with accuracies of 1%, all without bulky gas burets or any corrections for pressure and temperature.

The atmospheric pressure operation also has many significant advantages. Since the seals are subjected to little or no pressure differentials, the possibilities for leaks are greatly reduced. Furthermore, should a leak develop, the internal pressure will be restored to atmospheric and the mercury seal will then prevent additional borohydride from entering the generator. The operator can tell at a glance how far the hydrogenation proceeded before the leak occurred, remedy the situation, and proceed with the hydrogenation. Should the catalyst become inactive, fresh catalyst can be prepared and added to the hydrogenation flask without interrupting the hydrogenation. Observation of the height of the mercury column in the central tube of the bubbler gives a rapid, sensitive indication of whether or not the hydrogenation is proceeding. Finally, if the reaction becomes too vigorous, the solvent vaporizes, reducing the hydrogen partial pressure and decreasing the rate of the reaction. Any sudden increase in pressure is exhausted through the bubbler, avoiding rupture of the assembly.

The use of sodium borohydride solutions as a source of hydrogen is a marked convenience over the cylinder. First, it is less bulky and safer to store than gas cyl-

inders. Second, it allows the storage of more hydrogen in a given volume. One liter of a 5 *M* sodium borohydride solution, readily stored in a glass vessel, can provide 20 moles (about 500 l.) of hydrogen. Thus large scale hydrogenations can be carried out automatically, without the need for constant supervision to refill hydrogen reservoirs of limited capacity. Finally, the sodium borohydride provides a source of exceedingly pure hydrogen. We have never encountered the need to introduce a purification train.

The new hydrogenation technique allows the catalyst to be made reproducibly, since it is not exposed to laboratory air. This can be a significant factor in laboratories near sources of fumes containing sulfur compounds or amines.

All in all, this hydrogenator and the new hydrogenation technique appear to offer advantages which should prove of great utility and convenience to organic chemists.[10]

Experimental Section

General Procedure.—For internal hydrogenation, the following procedure is representative.

(1) Place 100 ml of ethanol, 5 ml of a 0.2 *M* solution of chloroplatinic acid in ethanol, and 5 g of Darco K-B or G-60 carbon in a 500-ml special erlenmeyer flask equipped for magnetic stirring. (2) Attach the flask to the hydrogenator which is assembled for internal hydrogenation and flush with nitrogen[11] (see Figure 3). (3) Place 150 ml of 1.0 *M* sodium borohydride solution in ethanol in the buret. (4) With vigorous stirring, inject 20 ml of 1.0 *M* sodium borohydride solution in ethanol into the reaction mixture to prepare the catalyst. (5) Inject 20 ml of concentrated hydrochloric acid (or 10 ml of glacial acetic acid). (6) Inject 500 mmoles of the olefin.

For external hydrogenation, the following procedure is representative.

(1) Place 100 ml of ethanol, 5 ml of a 0.2 *M* solution of chloroplatinic acid in ethanol, and 5 g of Darco K-B or G-60 carbon in a 500-ml special erlenmeyer flask equipped for magnetic stirring. (2) Attach the flask to the hydrogenator assembled for external hydrogenation and flush with nitrogen (see Figure 2). (3) Place 150 ml of 1.0 *M* sodium borohydride solution, 1.0 *M* in sodium hydroxide, in the buret. (4) With vigorous stirring, inject 20 ml of 1.0 *M* sodium borohydride solution in ethanol into the reaction mixture to prepare the catalyst. (5) Inject 5 ml of concentrated hydrochloric acid (or 4 ml of glacial acetic acid) into the reactor. (6) Inject 30 ml of 1.0 *M* sodium borohydride solution into the generator to purge the system. (7) Inject 500 mmoles of the olefin into the reactor. Certain hydrogenations, such as diethyl maleate are very dependent upon an excess of strong acid, and more hydrochloric acid may be used in either the internal or external hydrogenation procedure.

If the catalyst is to be used in a solvent other than ethanol, the above procedure is modified as follows after step 5.

(a) Remove the flask containing the catalyst from the hydrogenator and pour the contents into a sintered-glass Büchner funnel. (b) With suction, remove most of the ethanol, leaving about $^1/_8$ in. to cover the catalyst. (c) Add 50 ml of ethanol to the catalyst and stir with a spatula. Repeat the suction and washing steps until the catalyst has been washed once with 50 ml of ethanol and thrice with 50 ml of the new solvent. (d) Using a wash bottle, wash the catalyst into a hydrogenation flask with 100 ml of the new solvent. (e) Connect the flask to the hydrogenator and proceed with steps 6 and 7. It may be convenient on very large-scale runs to pour the substrate into the reactor before the final purging of the system, rather than injecting.

(10) The hydrogenator is readily adapted to the quantitative generation of other gases: hydrogen chloride for the hydrochlorination of reactive alcohols and olefins [H. C. Brown and M.-H. Rei, *J. Org. Chem.*, **31**, 1090 (1966)], and carbon monoxide for the carbonylation of borane and trialkylboranes [M. W. Rathke, *J. Am. Chem. Soc.*, **88**, 2870 (1966)].

(11) Although we routinely used such a nitrogen flush, it does not appear to be essential.

For the 40-mmoles hydrogenations, the following quantities of reagents were used: 40 ml of ethanol solvent in a 125-ml flask, 1.0 ml of 0.20 *M* chloroplatinic acid solution in ethanol, 1.0 g of carbon, 5.0 ml of 1.0 *M* ethanolic borohydride solution to prepare the catalyst 1.0 ml of 12 *N* hydrochloric acid to destroy excess borohydride after catalyst preparation (2.0 ml for internal hydrogenation), 10.0 ml of 1.0 *M* borohydride solution to purge the system (external hydrogenations only). When the catalyst was being transferred to another solvent, it was washed once with 20 ml of ethanol and thrice with 20 ml of the new solvent. Then it was washed into a hydrogenation flask with 40 ml of the new solvent.

Solutions and Materials.—The 1.0 *M* ethanolic sodium borohydride solution was prepared by dissolving 3.95 g of the solid in a solvent consisting of 5 ml of 2 *N* aqueous sodium hydroxide and 95 ml of ethanol. The solution was filtered and stored at 0°. Standardization was done by measuring the gas evolved when 10.0 ml of this solution was added to acid. Alternatively, the solution could be standardized by carrying out a hydrogenation of a standard olefin, such as 1-octene.

The 1.0 *M* aqueous sodium borohydride solution was prepared by dissolving 9.45 g of the solid and 10.0 g of sodium hydroxide in 200 ml of water and diluting to 250 ml. After filtration, the solution was standardized by the same procedure as was the ethanolic solution. This aqueous solution lost about 1% of its hydrogen content every 48 hr at room temperature.

The 0.20 *M* ethanolic solution of chloroplatinic acid was prepared by dissolving 1.0 g of the solid in 10.0 ml of ethanol. The reagents and their sources are listed as follows: sodium borohydride, Metal Hydrides, Inc., $NaBH_4$, 98%; chloroplatinic acid, Engelhard Industries, Inc., H_2PtCl_6, 40% platinum by weight; carbon, Atlas Powder Co., Darco K-B or G-60 grade activated carbon.

The unsaturated compounds were all commercially available chemicals whose physical properties were checked and which were purified in cases where this appeared necessary.

1-Octene.—Five hundred mmoles (78.8 ml, 56.0 g) of Phillips 99% 1-octene, $n^{20}D$ 1.4093, was hydrogenated internally in ethanol solvent at 25° in about 1 hr. The reaction mixture was filtered with suction and poured into 500 ml of 10% calcium chloride solution. This was extracted three times with 50 ml of pentane. The extracts were dried and distilled. A total of 43.9 g, 77%, of *n*-octane, bp 124°, $n^{20}D$ 1.3983, was obtained.

β-Pinene.—Five hundred mmoles (78.5 ml, 68.0 g) of β-pinene ($n^{20}D$ 1.4617) from the Glidden Co., 91.5% optically pure, was hydrogenated internally in ethanol solvent at 25° in about 2 hr. The first 90% hydrogenated much more rapidly than the last 10%, probably owing to isomerization of β- to α-pinene and slow hydrogenation of the latter. Owing to the sensitivity of the compound, acetic acid was used instead of hydrochloric. The reaction mixture was filtered with suction, poured into 1000 ml of ice water, and extracted with methylene chloride (one 100-ml and two 50-ml portions). The extracts were dried and fractionated. A yield of 60.0 g, 87%, of (−)-pinane was obtained, bp 164–166°, $n^{20}D$ 1.4618, $[\alpha]D$ −21.3°. The product was 80% *cis* and 20% *trans* isomer.

Diethyl Maleate.—Five hundred mmoles (81 ml, 86 g) of diethyl maleate, $n^{20}D$ 1.4416, was hydrogenated internally in ethanol solvent in about 90 min. The reaction product was filtered with suction and poured into 100 ml of cold 5% sodium bicarbonate solution. This solution was extracted once with 50 ml and nine times with 25 ml of methylene chloride. The extracts were dried and fractionated, a yield of 77.6 g, 90%, of diethyl succinate, bp 103–105° (15 mm), $n^{20}D$ 1.4201, being obtained.

Ethyl Oleate.—Five hundred mmoles (155 g) of ethyl oleate (Matheson Coleman and Bell), $n^{20}D$ 1.4531, was hydrogenated externally in ethanol solvent in about 2 hr. The reaction product was filtered and poured slowly into about 50 ml of ice water. The white solid obtained was collected and melted, and the lower layer of water was removed with a syringe. The yield of ethyl stearate, mp 29–32°, was 144 g, 92%.

Five hundred grams (1600 mmoles) of ethyl oleate was similarly hydrogenated in 200 ml of ethanol over 3.0 mmoles of carbon-supported platinum. The reaction required about 4 hr, with two further additions of 1.0 mmole of catalyst being required to overcome poisoning (addition was done by injecting a slurry with a hypodermic syringe). After completion, the reaction mixture was filtered and poured into about 1 l. of ice water.

The collected solid was treated as in the 500-mmole run (see above); a yield of 475 g, 95%, of ethyl stearate, mp 29–32°, was obtained.

1,5,9-Cyclododecatriene.—One hundred and fifty mmoles (450 mequiv), 27.5 ml, 24.3 g) of 1,5,9-cyclododecatriene (Cities Service), $n^{20}D$ 1.5049, was hydrogenated externally in ethanol solvent at 55° using a steam-heated water bath to maintain the temperature. The reaction was complete in about 1 hr. The reaction mixture was heated to boiling, filtered hot, and evaporated until only a white solid remained. This was dissolved in ether to remove salts. The ether solution was dried and the ether was evaporated, a yield of 21.8 g, 87% of cyclododecane, mp 59–61°, being obtained.

Norbornene-5,6-dicarboxylic Acid Anhydride.—Five hundred mmoles (82.0 g) of norbornene-5,6-dicarboxylic acid anhydride (Eastman, White Label), mp 164°, was hydrogenated in dry tetrahydrofuran by the external procedure in just over 1 hr. The reaction mixture was filtered and most of the tetrahydrofuran removed by distillation. After recrystallization from the hexane, a yield of 74.4 g, 90%, of the saturated anhydride, mp 167°, was obtained. The infrared spectrum showed no bands at 5.9 μ indicating the absence of acid.

Benzalacetone.—Five hundred mmoles of benzalacetone (Eastman, White Label), recrystallized from pentane–ethyl acetate, mp 39°, was hydrogenated in ethanol solvent by the external procedure at 25°. The reaction, which required 1 hr, was run in the presence of acetic acid only, since strong acid greatly promotes hydrogenolysis of the carbonyl group. The reaction mixture was filtered and the ethanol was removed by distillation. The residue was dissolved in 300 ml of ether, then washed with water. The ether extract, dried over magnesium sulfate, was subjected to flash distillation to remove the ether. The residue was distilled through a 30-cm Vigreaux column. A yield of 69.2 g, 92%, of saturated phenyl ketone, bp 233–235°, $n^{20}D$ 1.5105, was obtained. The infrared spectrum showed a small band at 2.8 μ (OH); so the product was subjected to gas chromatographic analysis. This analysis showed 93% 1-phenyl-3-butanone, 6% 1-phenyl-3-butanol, and 1% *n*-butylbenzene. This ratio would indicate the uptake of 540 mmoles of hydrogen, the amount actually absorbed.

Cholesterol.—The hydrogenation of 8.3 g (21.5 mmoles) of cholesterol (Eastman, White Label), mp 150°, over 0.33 g of commercial PtO_2 (Adams catalyst) was carried out using the hydrogenator assembled for external hydrogenation. The substrate was dissolved in 110 ml of ethyl acetate containing 4 drops of 70% perchloric acid. This solution was placed in the reactor flask with the catalyst. The system was flushed with hydrogen and reaction was begun. Twenty minutes was required for complete hydrogenation. The reaction mixture was filtered to remove the catalyst, and about half of the solvent was removed. The remaining solution was allowed to stand at −10° for 2 days and the resulting solid was collected. A yield of 6.8 g, 81%, of cholestanol, mp 137–139°, was obtained. Hershberg, *et al.*,[9] report that about 1–2% each of coprostane, cholestane, and coprostanol are formed as side products.

Agitation.—Agitation for the rate runs was provided by a small LaPine magnetic stirrer. The stirrer's rheostat was set at 8.5 for internal hydrogenations and 10 for external hydrogenations. For the preparative runs, a large Precision Scientific Co. Senior Mag-Mix stirrer was employed.

Acknowledgment.—This study was assisted in part by a grant from Parke, Davis & Co.

Conformational Preference in Ring A of 5(10)-Unsaturated Steroids[1a]

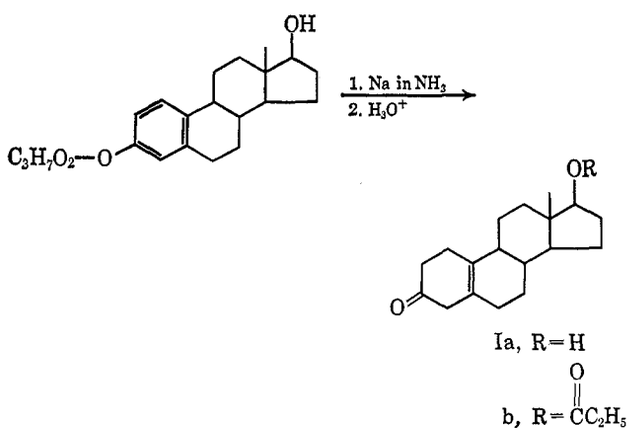
SAMUEL G. LEVINE,[1b] NANCY H. EUDY, AND CONSTANCE F. LEFFLER

Department of Chemistry, North Carolina State University, Raleigh, North Carolina, and Natural Products Laboratory, Research Triangle Institute, Durham, North Carolina

Received June 27, 1966

The hydride reduction of a $\Delta^{5(10)}$-3-keto steroid is found to be highly stereoselective, producing mostly the 3α-alcohol. This result is rationalized in terms of a preferred half-chair ring-A conformation (Xb) which is further supported by physical evidence.

A practical route to 5(10)-unsaturated steroids was not available until 1949 when Birch and Mukherji[2] reported the preparation of keto alcohol Ia *via* sodium in ammonia reduction of estradiol-3-glyceryl ether. Such



Ia, R = H

b, R = $\overset{O}{\overset{\|}{C}}C_2H_5$

β,γ-unsaturated ketones have since served as versatile intermediates for the preparation of nonaromatic 19-nor steroids of various structural types. Improvements of the original procedures are abundant and were spurred on, no doubt, by the great pharmacological importance of these end products. Recent developments have been reviewed both from the chemical[3,4] and biological[4] points of view.

Most of the above investigations have not been of such nature as to give insight into the *stereochemistry* of ring A in 5(10)-unsaturated steroids. A notable exception, however, is provided by Hartman's report[5] on the lithium aluminum hydride reduction of ketone Ia. We believe that the results of this experiment (described below) point to the operation of certain novel stereochemical effects in ring A of 5(10)-unsaturated steroids; our efforts toward elucidating these effects are described in this paper.[6]

The reduction of ketone Ia with ethereal lithium aluminum hydride was found[5] to produce a *single* 3,17β-diol in 77% yield; the purified product, mp 208–209°,

(1) (a) This work was supported by the National Institutes of Health, U. S. Public Health Service under Grant AM 09279 from the National Institute of Arthritis and Metabolic Diseases and Contract SA-43-ph-4351 from the Cancer Chemotherapy National Service Center; (b) Department of Chemistry, North Carolina State University, Raleigh, N. C.

(2) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949).

(3) F. J. Kakis in "Steroid Reactions—an Outline for Organic Chemists," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, Chapter 6.

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 18.

(5) J. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955).

(6) A portion of these results has been reported in preliminary form: S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963).